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FORMULATION AND EVALUATION OF ATORVASTATIN MOUTH DISSOLVING TABLETS

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ABSTRACT

The formulation and development of an orally disintegrating tablet (ODT) for atorvastatin, a widely used statin for managing hyperlipidemia, offers several advantages, including improved patient compliance, easy of administration, and rapid onset of action. The development of atorvastatin ODT involves addressing challenges related to the drug's stability, taste masking, and optimal disintegration characteristics. The primary objective is to develop a fast-dissolving formulation that ensures effective drug delivery and minimal side effects. In this study, different excipients such as superdisintegrants, binders and flavouring agents were systematically selected to enhance the dissolution rate and mask the bitter taste of atorvastatin. The physicochemical properties, including hardness, disintegration time and dissolution rate, were thoroughly evaluated. The final formulation exhibited satisfactory disintegration and dissolution profiles, with rapid release of atorvastatin, ensuring faster bioavailability.

KEYWORDS

HMG-COA reductase inhibitor, Antihyperlipidemicagent, (Lipitor®) is a liquid lowering drug and It reduce the risk of cardiovascular disease.

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INTRODUCTION

In the recent past, several new advanced technologies have been introduced for the formulation of mouth dissolving tablets (MDTs) with very interesting features, like extremely low disintegration time, exceptional taste masking ability, pleasant mouth feel and sugar free tablets for diabetic patients. The technologies utilized for

fabrication of MDDDS include lyophilization, moulding, direct compression, cotton candy process, spray drying, sublimation, mass extrusion, nanoionization and quick dissolve film formation. These techniques are based on the principles of increasing porosity and/or addition of superdisintegrants and water soluble excipients in the tablets. The formulations prepared from these techniques differ from each other on the basis of the factors like mechanical strength of final product, drug and dosage form stability, mouth feel, taste, rate of dissolution of the formulation in saliva, rate of absorption from saliva and overall drug bioavailability.

Although, numerous technologies had been developed for the fabrication of these uniques dosage forms in last two decades, but so far, no standardized technique has been designed or mentioned in pharmacopoeias for their evaluation except in European Pharmacopoeia (EP), which defines orodispersible tablets as "uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed". EP also specifies that the orodispersible tablets should disintegrate within 3 minutes when subjected to conventional disintegration test used for tablets and capsules.

Evaluation of Atorvastatin Granules

Angle of Repose

Angle of repose is defined as the maximum angle possible between the surface of the pile of powder and horizontal plane. The angle of repose of the power or granules was determined by fixed funnel method to assess the flow property of the powder or granules

Bulk Density and Tapped Density

Bulk density is the ratio between a given mass of powder or granules and its bulk volume. Tapped density is the ratio between a given mass of powder or granules and the constant or fixed volume of the powder or granules after tapping. An accurately weighed quantity of granules (W) (which was previously passed through sieve no. 40) was carefully transferred into 250 ml measuring cylinder and initial volume (V_o) was measured.

Bulkiness

Reciprocal of bulk density is known as bulkiness. It is expressed by cc/gm.

Bulkiness =1/Bulk Density

Compressibility Index and Hausner Ratio

In recent years, the compressibility index and the closely related Hausner ratio have become the simple, fast, and popular methods of predicting powder flow characteristics. The compressibility index has been proposed as an indirect measure of bulk density, size and shape, surface area, moisture content and cohesiveness of materials, because all of these can influence the observed compressibility index.

DISCUSSION

The present study was undertaken to formulate Atorvastatin Oral Disintegrating Tablets with two Superdisintegrants namely CCS and SSG and (CCS + SSG), in three different ratios and by wet granulation technique. Before compression of the granules physical characters such as, bulk density, tapped density, bulkiness, angle of repose, compressibility index and Hausner ratio were determined and tabulated in the Table No.3. Then the granules were compressed into tablets and then evaluated. The results are presented in Table No.4.

Evaluation of prepared Atorvastatin granules

Bulk density

The bulk density of all formulations was measured by using measuring cylinder. The bulk density was found in the range of 0.37 $\pm$ 0.8 - 0.40 $\pm$ 0.02gm/cm^3.

Tapped Density

The tapped density of all formulations was determined by using measuring cylinder. The tapped density was found in the range 0.40 $\pm$ 0.02 – 0.47 $\pm$ 0.04gm/cm^3.

Bulkiness

The bulkiness of all formulations was found in the range between 2.52$\pm$11–2.72$\pm$0.11cc/gm.

Angle of Repose

The angle of repose of all the formulations was within 31.97^{o}- 32.58^{o}. If the angle of repose is within 35^{o}, it indicates good flow property of the granules[166]. The result showed that the granules of all formulations showed good flow properties.

Compressibility Index (CI)

If the compressibility index of the granules is between 11-15%, it shows good flow character. All the formulations showed the CI was in the range between 11.88–14.84. It indicates that the granules showed good flow character.

Hausner Ratio

The result of the Hausner ratio of all the formulations was between 1.14–1.18. If the Hausner ratio lies between 1.15 – 1.18, it showed good flow behavior of the granules or powder. The result indicates that all formulations showed good flow property

Evaluation of Atorvastatin Oral Disintegrating Tablets

The compressed tablets were evaluated for physical properties and the results are tabulated in Table No.4.

Hardness

The hardness was in the range of 3.60±0.14 to 3.84±0.17kg/cm^{2}. It was within the acceptable limits

Uniformity of weight

Uniformity of weight was found to be in the range of 193.25±0.606 to 200.5.30±0.006mg. It was with in the acceptable limits.

Friability

The friability of all the formulation was within 1% which was in the range of 0.40±0.12to 0.55 ±0.18%. It was with in the acceptable limits.

Wetting time

The wetting time for all the formulated tables was in the range of 39.6 ± 1.22 to 161.4 ± 2.41 sec.

Disintegration time

The disintegration time of all the formulated tablets was between 13.5 ± 1.84 to 135 ± 1.58 sec.

***In vitro* dispersion time**

The *in vitro* dispersion time for F-1 to F-7 formulation was found to be in the range of 46.4 ± 0.55 to 212.6 ± 1.14 sec.

Drug content

The drug content was in the range of 98.20±0.46 to 100.24±0.46%. It was within the acceptable limits.

IR Spectral Analysis

The IR spectra revealed that the drug is compatible with the superdisintegrants. The peaks and pattern of pure drug (Atorvastatin) and with highest proportion of (5%w\w) superdisintegrant (5%) showed that there was no interaction of Atorvastatin with the polymers.

***In vitro* release studies**

F-3, F-6 and F-7 formulations were selected for the *in vitro* release studies because the disintegration time for these three formulations was within a minute. The *in vitro* release study for the formulations F-3, F-6 and F-7 were shown in Table No.5 and in the Figure No.2. The *in vitro* release study shows that about 94.5% and 98% of drug was released in F-3 and F-6 formulations in 4 min. But in F-7 formulation 99% of drug was released within 3 min. It showed that the combination of cross carmellose sodium and sodium starch glycolate increased the percentage of drug release within 3 minutes.

***In vitro* release study of F-3, F-6 and F-7 formulations**

Time(min)	Percentage Drug Release		
	F-3	F-6	F-7
1	18	20	31.5
2	36	41	67.5
3	63	66	99
4	94.5	98	-

Table No.1: Standard curve of Atorvastatin

S.No	Concentration (ug/ml)	Absorbance at 265nm
1	0	0.000
2	10	0.249
3	15	0.364
4	20	0.471
5	25	0.631
6	30	0.731
7	35	0.921

Table No.2: Formulation of Atorvastatin mouth dissolving tablets

S.No	Ingredients (mg)	F1 (1:0.25)	F2 (1:0.5)	F3 (1:0.75)	F4 (1:0.25)	F5 (1:0.5)	F6 (1:0.75)	F7 (1:0.75)
1	Atorvastatin	20	20	20	20	20	20	20
2	Croscarmellose sodium	5	10	15	-	-	-	-
3	Sodium starch glycolate	-	-	-	5	10	15	-
4	Croscarmellose sodium + Sodium starch glycolate	-	-	-	-	-	-	15
5	Microcrystalline cellulose	113	108	103	113	108	103	103
6	Mannitol	50	50	50	50	50	50	50
7	Aspartame	8	8	8	8	8	8	8
8	Isopropyl alcohol	q.s	q.s	q.s	q.s	q.s	q.s	q.s
9	Magnesium stearate	4	4	4	4	4	4	4
10	Menthol	q.s	q.s	q.s	q.s	q.s	q.s	q.s
11	Total weight of one tablet	200	200	200	200	200	200	200

Table No.3: Evaluation of prepared Atorvastatin granules

Formulatin code	Angle of repose(θ)	Bulk density (gm/cc)	Tapped density (gm/cc)	Bulkiness (cc/gm)	Compressibility index (%)	Hausner ratio
F-1	31.97 ±0.53	0.38 ±0.02	0.44 ±0.04	2.56 ±0.17	13.88 ±3.56	1.16 ±0.05
F-2	32.09 ±0.65	0.40 ±0.02	0.47 ±0.04	2.52 ±0.11	14.36 ±3.78	1.17 ±0.05
F-3	32.58 ±1.12	0.37 ±0.02	0.42 ±0.02	2.64 ±0.17	11.88 ±3.84	1.15 ±0.05
F-4	32.07 ±0.79	0.37 ±0.03	0.44 ±0.05	2.68 ±0.18	14.21 ±5.52	1.18 ±0.08
F-5	32.15 ±0.92	0.37 ±0.02	0.44 ±0.04	2.68 ±0.11	14.95 ±5.47	1.18 ±0.08
F-6	32.45 ±1.27	0.37 ±0.02	0.40 ±0.02	2.68 ±0.11	14.09 ±4.95	1.18 ±0.07
F-7	32.21 ±0.67	0.37 ±0.02	0.43 ±0.03	2.72 ±0.11	14.84 ±4.88	1.16 ±0.08

Table No.4: Evaluation of prepared Atorvastatin Oral Disintegrating Tablets

Formulation code	Hardness[a] (kg/cm^2)	Uniformity of weight[b](mg)	Friability[c](%)	Wetting time[a] (sec)	Water absorption ratio[a] (%)	Disintegration time[a] (sec)	Dispersion time[a](sec)	Drug content[c] (%)
F-1	3.72 ± 0.11	194.60 ± 0.005	0.55 ± 0.18	111.6 ± 2.70	75.28 ± 2.18	97.6 ±1.14	143.6 ± 1.52	98.88 ± 0.44
F-2	3.76 ± 0.09	199.95 ± 0.006	0.55 ± 0.14	80.8 ± 2.39	123.67 ± 1.86	71.6 ±0.55	97.6 ± 0.89	98.20 ±0.66
F-3	3.72 ± 0.11	200.15 ± 0.006	0.45 ± 0.10	44 ± 1.58	134.26 ± 2.23	35.8 ±1.30	56.2 ± 0.84	99.52 ± 0.33
F-4	3.60 ± 0.14	193.25 ± 0.006	0.44 ± 0.11	106 ± 1.22	82.64 ± 6.94	80.8 ±0.84	122 ± 2.12	98.32 ± 0.72
F-5	3.64 ± 0.22	195.75± 0.006	0.43 ± 0.11	75.8 ± 1.30	123.82 ± 1.26	67.2 ±1.79	89.8 ± 1.30	97.72 ±0.74
F-6	3.84 ± 0.17	197.00 ± 0.003	0.40 ± 0.12	39.6 ± 1.52	146.99 ± 4.83	14.8 ±0.84	46.4 ± 0.55	100.24 ±0.46
F-7	3.80 ± 0.24	197.65 ± 0.005	0.42 ± 0.10	161.4 ± 2.41	61.74 ± 3.03	13.5 ±1.58	212.6 ± 1.14	99.04 ±0.67

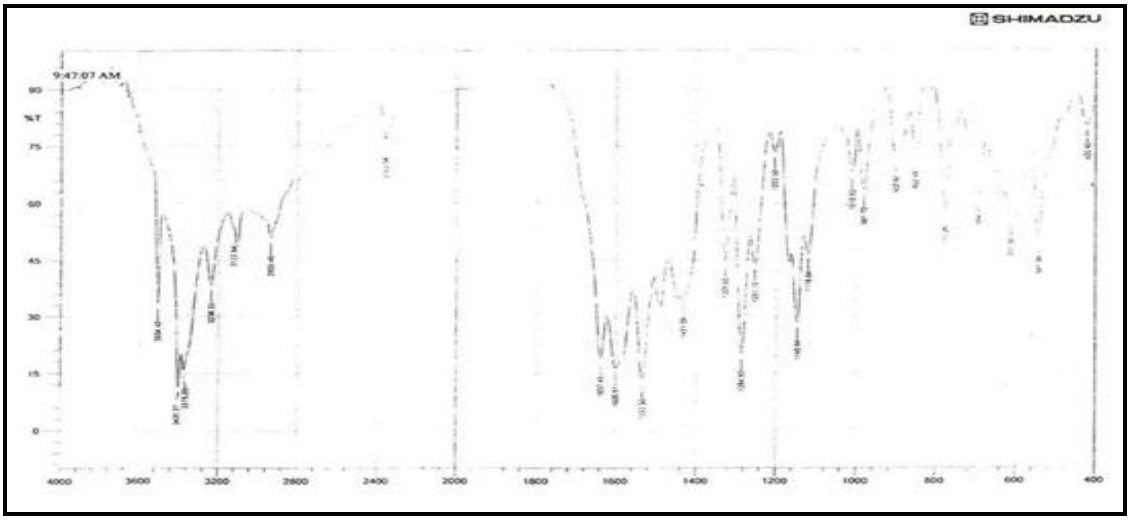

Figure No.1: IR Spectra of Pure Atorvastatin

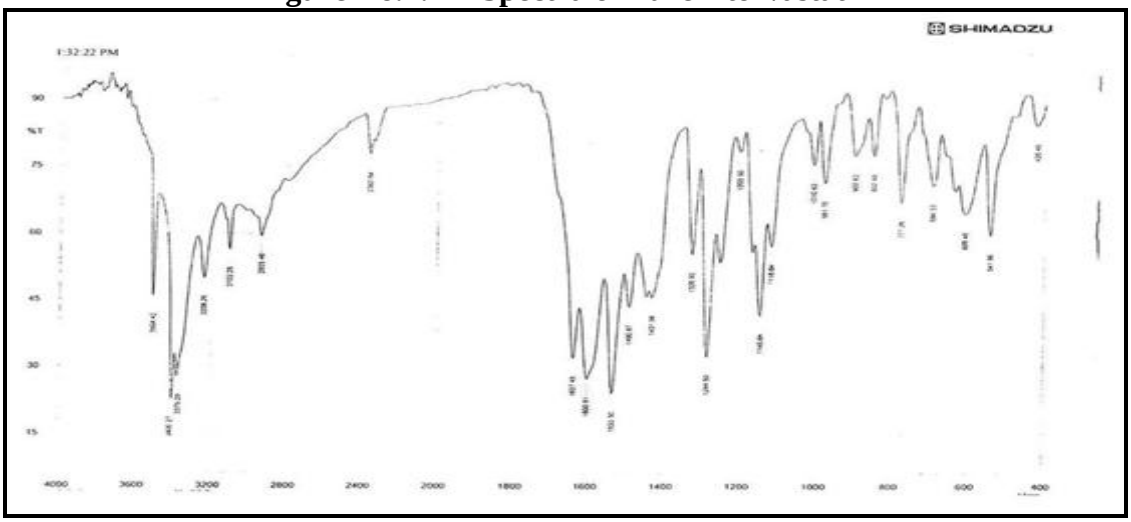

Figure No.2: IR Spectra of sodium starch glycolate (5%w/w)

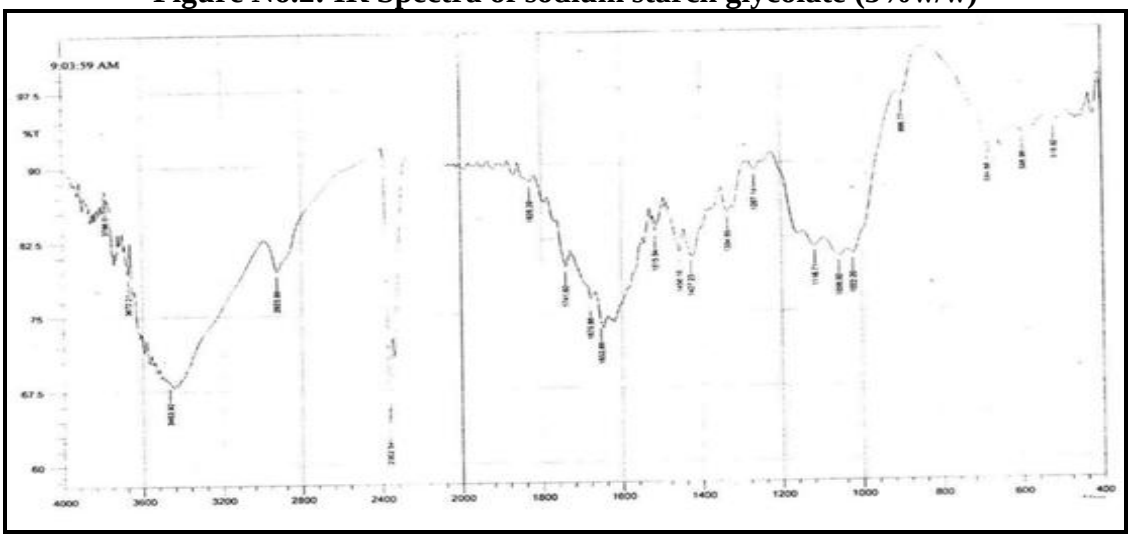

Figure No.3: IR Spectra of croscarmellose sodium (5%w/w)

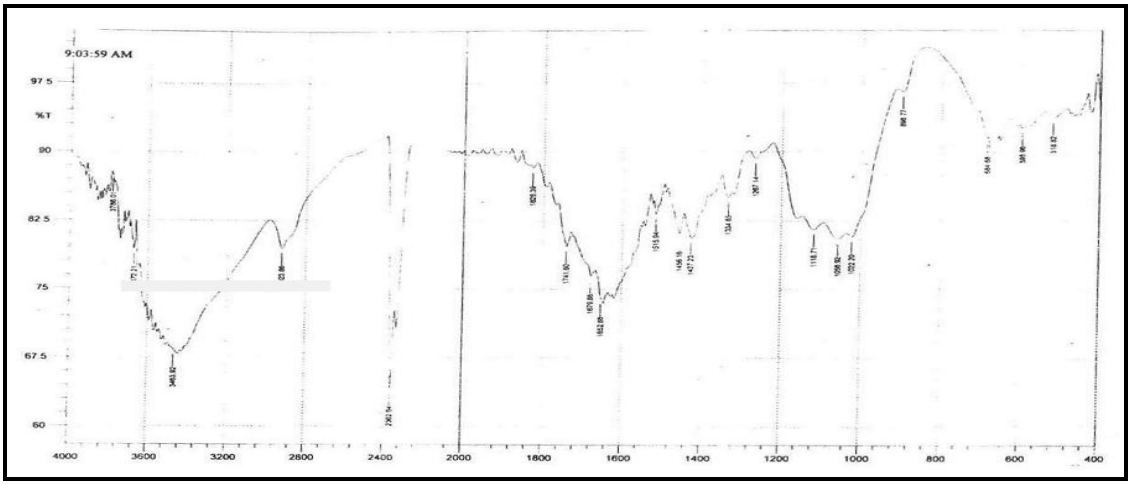

Figure No.4: IR Spectra of Atorvastatin +5%SSG

CONCLUSION

The release of drug from the F-7 formulation was quick when compared to F-3 and F-6 formulation. All the results proved that Oral Disintegrating Tablets of Atorvastatin may enhance the patient compliance, low dosing, rapid onset of action, increased bioavailability, low side effect and good stability. Further studies of ODT of Atorvastatin may prove popularity in future.

The ODTs have potential advantages over conventional oral dosage forms with their improved patient compliance; convenience, bioavailability and rapid onset of action which drawn the attention of many manufactures over a decade. ODT formulations obtained by some of these technologies have sufficient mechanical strength, quick disintegration/dissolution in the mouth. Many drugs can be incorporated in ODT especially unpalatable drugs. The research is still going on. More products need to be commercialized to use this technology properly. Thus ODT may be developed for most of the available drugs in near.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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